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EXAMINER
HILL, KEVIN KAI

ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/757,345	AGRAWAL ET AL.	
	Examiner	Art Unit	
	KEVIN K. HILL	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *February 17, 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1, 3,5,10-15,18,31-32,40,42,95,99,147-148 and 150-153* is/are pending in the application.

4a) Of the above claim(s) *3,5,10-15,18,32,40,42,95,99,147 and 150-153* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,31 and 148* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Election/Restrictions

Applicant has elected the invention of Group I, drawn to an immunomer compound comprising at least two oligonucleotides linked together, wherein Applicant has elected the oligonucleotide linkage species to be "iv", a sugar to a non-nucleotide linker and the "G" moiety species to be "2'-deoxy-7-deazaguanosine". However, upon further consideration, the Examiner has withdrawn the "G" species election requirement.

Election of Applicant's invention(s) was made without traverse.

Amendments

Applicant's response and amendments, filed February 17, 2010, to the prior Office Action is acknowledged. Applicant has cancelled Claims 2, 4, 6-9, 16-17, 19-30, 33-39, 41, 43-94, 96-98, 100-146 and 149, withdrawn Claims 3, 5, 10-15, 18, 32, 40 and 42, 95, 99 and 147, amended Claims 1, 3, 5, 95, 99 and 148, and added new claims, Claims 150-153.

Claims 3, 5, 10-15, 18, 32, 40, 42, 95, 99, 147 and 150-153 are pending but withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected invention, there being no allowable generic or linking claim.

Claims 1, 31 and 148 are under consideration.

Response to Amendment

The Examiner acknowledges Applicant's request for rejoinder of presently withdrawn claims. However, Claim 1 is not yet in condition for allowance for reasons discussed below.

Claim Objections

1. **The reply filed on February 17, 2010 is not fully responsive to the prior Office Action** because of the following omission(s) or matter(s):

The amendments to the claims do not comply with the Revised Amendment Practice of 37 CFR 1.121 (See OG Notice 23 September 2003). Specifically, a list of all claims should be submitted, the text of withdrawn claims must be included in the listing of the claims and the text of canceled claims must be omitted.

§1.121 Manner of making amendments in applications.

(c) Claims. Amendments to a claim must be made by rewriting the entire claim with all changes (e.g., additions and deletions) as indicated in this subsection, except when the claim is being canceled. Each amendment document that includes a change to an existing claim, cancellation of an existing claim or addition of a new claim, must include a complete listing of all claims ever presented, including the text of all pending and withdrawn claims, in the application. The claim listing, including the text of the claims, in the amendment document will serve to replace all prior versions of the claims, in the application. In the claim listing, the status of every claim must be indicated after its claim number by using one of the following identifiers in a parenthetical expression: (Original), (Currently amended), (Canceled), (Withdrawn), (Previously presented), (New), and (Not entered).

(2) When claim text with markings is required. All claims being currently amended in an amendment paper shall be presented in the claim listing, indicate a status of "currently amended," and be submitted with markings to indicate the changes that have been made relative to the immediate prior version of the claims. The text of any added subject matter must be shown by underlining the added text. The text of any deleted matter must be shown by strike-through except that double brackets placed before and after the deleted characters may be used to show deletion of five or fewer consecutive characters. The text of any deleted subject matter must be shown by being placed within double brackets if strike-through cannot be easily perceived. Only claims having the status of "currently amended," or "withdrawn" if also being amended, shall include markings. If a withdrawn claim is currently amended, its status in the claim listing may be identified as "withdrawn- currently amended."

The correct status of Claims 3, 5, 95 and 99 are “Withdrawn—Currently Amended".

Priority

Applicant’s claim for the benefit of a prior-filed parent provisional application 60/440,587 filed on January 16, 2003 under 35 U.S.C. 119(e) is acknowledged.

Accordingly, the effective priority date of the instant application is granted as January 16, 2003.

Examiner's Note

Unless otherwise indicated, previous objections/rejections that have been rendered moot in view of the amendment will not be reiterated. The arguments in the February 17, 2010 response will be addressed to the extent that they apply to current rejection(s).

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 103

2. **The prior rejection of Claims 1, 31 and 148 under 35 U.S.C. 103(a)** as being unpatentable over Yu et al (2000; *of record in IDS) in view of Kandimalla et al (2001; *of record in IDS) and Liu et al (2001; *of record) and Yu et al (N.A.R. 30(20):4460-4469, 2002; *of record in IDS) **is withdrawn** in preference for the rejection set forth below.

3. **Claims 1, 31 and 148 are rejected under 35 U.S.C. 103(a)** as being unpatentable over Yu et al (2000; *of record in IDS) in view of Kandimalla et al (2001; *of record in IDS), Liu et al (2001; *of record) Yu et al (2002; *of record in IDS), Krieg (U.S. 2004/0053880; of record) and Wise et al (U.S. 2004/0009933).

This is a new rejection.

Determining the scope and contents of the prior art.

The teachings of Yu et al (2000), Kandimalla et al (2001), Liu et al (2001) and Yu et al (2002) are discussed in the prior Office Action, and incorporated herein.

Krieg disclosed immunostimulatory oligonucleotides in which the cytosine of a CpG motif is substituted for a P-base and the guanosine may be substituted for a purine base analog of guanine, e.g. 7-deazaguanine. The pyrimidine base analog of cytosine can replace cytosine without impairing the immunostimulatory activity of the oligonucleotide. Similarly, the modified guanine can replace guanine without impairing immunostimulatory activity [0094].

Ascertaining the differences between the prior art and the claims at issue, and Resolving the level of ordinary skill in the pertinent art.

People of the ordinary skill in the art will be highly educated individuals such as medical doctors, scientists, or engineers possessing advanced degrees, including M.D.'s and Ph.D.'s. Thus, these people most likely will be knowledgeable and well-read in the relevant literature and have the practical experience in functional equivalents and analogues of nucleic acids and

chemical synthesis of immunostimulatory oligonucleotides. Therefore, the level of ordinary skill in this art is high.

"A person of ordinary skill in the art is also a person of ordinary creativity, not an automaton." *KSR International Co. v. Teleflex Inc.*, 550 U.S. ___, ___, 82 USPQ2d 1385, 1397 (2007). "[I]n many cases a person of ordinary skill will be able to fit the teachings of multiple patents together like pieces of a puzzle." *Id.* Office personnel may also take into account "the inferences and creative steps that a person of ordinary skill in the art would employ." *Id.* at ___, 82 USPQ2d at 1396.

Considering objective evidence present in the application indicating obviousness or nonobviousness.

It would have been obvious to one of ordinary skill in the art to substitute the 3'-3' internucleoside linkage of Yu et al (2000) with a non-nucleotidic internucleoside linkage as taught by Yu et al (2002) with a reasonable expectation of success because the simple substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention. M.P.E.P. §2144.07 states "The selection of a known material based on its suitability for its intended use supported a *prima facie* obviousness determination in *Sinclair & Carroll Co. v. Interchemical Corp.*, 325 U.S. 327, 65 USPQ 297 (1945)." When substituting equivalents known in the prior art for the same purpose, an express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. *In re Fout*, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). M.P.E.P. §2144.06. An artisan would be motivated to substitute the 3'-3' internucleoside linkage of Yu et al (2000) with a non-nucleotidic internucleoside linkage because Yu et al (2002) taught the C3 linker achieves an improved immune response than an immunomer without a non-nucleotidic linker.

It also would have been obvious to substitute a cytosine or first bicyclic non-natural cytosine analogue as taught by Kandimalla et al with a [second] bicyclic non-natural cytosine analogue, more specifically 2-oxo-7-deaza-8-methyl-purine (Liu et al), with a reasonable expectation of success because the simple substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention. M.P.E.P. §2144.07 states "The selection of a known material based on its suitability for its intended use supported a *prima facie* obviousness determination in *Sinclair & Carroll Co. v. Interchemical Corp.*, 325 U.S. 327, 65 USPQ 297 (1945) When substituting equivalents known in the prior art for the same purpose, an express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. *In re Fout*, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). M.P.E.P. §2144.06.

In the instant case, the prior art recognized that the P-base pyrrolocytosine (a.k.a. 2-oxo-7-deaza-8-methyl-purine) is an art-recognized cytosine analogue. An artisan would be motivated to substitute a the C* cytosine base for a non-natural nucleoside such as 2-oxo-7-deaza-8-methyl-purine because Krieg suggest substituting the cytosine of a CpG motif for a P-base in immunostimulatory oligonucleotides [0094], Liu et al teach that pyrrolocytosine is advantageous because it is intrinsically highly fluorescent, with excitation and emission maxima far from those of DNA and protein, making it ideal for probing protein-nucleic acid interactions (Liu et al, pg 466, col. 2, last ¶), i.e. studying the effects of sequence and structural changes in the flanking sequences that potentiate or suppress immunostimulatory activities of CpG oligos because the mechanism of immunostimulation by CpG oligonucleotides and the precise structural requirements and specific functional groups of cytosine and guanine necessary for recognition of and interaction with protein/receptor factors that are responsible for immune stimulation have not been elucidated (Kandimalla et al, Abstract). Similarly, Wise et al disclosed that pyrrolopyrimidine-C (aka pyrrolocytosine) is useful for investigating nucleic acid interactions with other nucleic acids and/or with proteins, and that researchers have long-desired fluorescent nucleosides to probe nucleic acid structure, and such fluorescent nucleoside bases also would be useful in the analysis of nucleic acid-protein interactions (Abstract, [0003]).

The ordinary artisan would have a reasonable expectation of success that an oligonucleotide comprising the cytosine analogue P-base pyrrolocytosine (a.k.a. 2-oxo-7-deaza-8-methyl-purine) instead of a cytosine in a CpG motif would be immunostimulatory because Krieg disclose that the pyrimidine base analog of cytosine can replace cytosine without impairing the immunostimulatory activity of the oligonucleotide and Wise et al disclosed that the pyrrolocytosine can substitute for cytosine without substantially altering the properties of nucleosides in which cytosine would normally be present. That is, replacement of cytosine with pyrrolopyrimidine-C does not substantially affect the functioning of the nucleoside in any substantial manner. Thus, replacement of cytosine with pyrrolopyrimidine-C is not believed to substantially alter the structure, e.g., secondary, tertiary or other structure, of any nucleic acid strand which substitutes one or more cytosines with one or more pyrrolopyrimidine-C molecules. Such properties provide for the ability to use pyrrolopyrimidine-C in place of cytosine in many

applications, such as…investigation of nucleic acid-protein interactions, investigation of nucleoside-protein interactions, for therapeutic uses, and the like [0007].

The cited prior art meets the criteria set forth in both *Graham* and *KSR*, and the teachings of the cited prior art provide the requisite teachings and motivations with a clear, reasonable expectation of success. Thus, absent evidence to the contrary, the invention as a whole is *prima facie* obvious.

Response to Arguments

Applicant argues that the mere fact that references can be combined or modified does not render the resultant combination obvious. One skilled in the art must have a reasonable expectation of success of reaching the instantly claimed invention. The claims are directed to an immunomer wherein at least one of the oligonucleotides comprises an immunostimulatory dinucleotide having the structure RpG. Therefore, the overly simplistic view that the prior art could be combined such that the C of the CpG dinucleotide could be replace with the pyrrolo-dC described in Liu is insufficient. Rather, there must be a reasonable expectation of success that such a modification would still be immunostimulatory. The cited art fails to provide such a reasonable expectation of success. Liu is completely silent regarding irnmunostimulatory oligonucleotides containing a CpG dinucleotide, or whether the dinucleotide can be modified, particularly with pyrrolo-dC, and still retain its irnrnunostimulatory activity.

Applicant's argument(s) has been fully considered, but is not persuasive.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

The prior art can be modified or combined to reject claims as *prima facie* obvious as long as there is a reasonable expectation of success. *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986) Obviousness does not require absolute predictability, however, at least some degree of predictability is required. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness. *In re Rinehart*, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976) See MPEP §2143.02.

In the instant case, Krieg disclose the cytosine (C*) of a C*pG motif may be substituted for a cytosine analogue, specifically a P-base [0094]. Wise et al disclosed that the pyrrolocytosine can substitute for cytosine without substantially altering the properties of nucleosides in which cytosine would normally be present. That is, replacement of cytosine with pyrrolopyrimidine-C does not substantially affect the functioning of the nucleoside in any substantial manner. Thus, replacement of cytosine with the cytosine analogue pyrrolopyrimidine-C is not believed to substantially alter the structure, e.g., secondary, tertiary or other structure, of any nucleic acid strand which substitutes one or more cytosines with one or more pyrrolopyrimidine-C molecules. Such properties provide for the ability to use pyrrolopyrimidine-C in place of cytosine in many applications, such as…investigation of nucleic acid-protein interactions, investigation of nucleoside-protein interactions, for therapeutic uses, and the like [0007]. Thus, at the time of the invention, those of ordinary skill in the art possessed a reasonable [emphasis added] expectation of success for an immunostimulatory oligonucleotide comprising 2-oxo-7-deaza-8-methyl-purine to retain immune stimulatory activity.

Applicant continues to argue that Kandimalla (2001) does not provide the motivation to substitute cytosine with pyrrolo-dc. Kandimalla (2001) teaches that a YpG-containing oligonucleotide in which Y was deoxy-P-base nucleoside (referred to as "the first bicyclic non-natural cytosine" by the Office Action) showed little or no immunostimulatory activity (see page 809, column 2, lines 22-24) (emphasis added) Dr. Kandimalla's declaration stated that such a modification rendered the compound inactive.

Applicant's argument(s) has been fully considered, but is not persuasive. The Examiner acknowledges the Kandimalla Declaration filed October 3, 2008 in which it is stated (¶5) that the phrase "showed little or no immunostimulatory activity" in reference to the P-base of Kandimalla (2001) meant that the modification was inactive. However, in response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Kandimalla teaches the substitution of a cytosine in a CpG motif for a P-base.

Thus, at the time of the invention, the concept of a P-base substitution in a CpG motif was known.

The problem in the field at the time of the invention comprises the elucidation of a structure/function relationship between a nucleic acid molecule and its protein receptor (Yu, Kandimalla). Applicant's own work (Kandimalla et al, 2001) clearly demonstrates that while not all cytosine analogue species may be functional as per the artisan's desired degree of efficacy, several species within a given genus are routinely tested/assayed for activity to draw a real-world, scientifically meaningful conclusion per the cytosine analogue genus. For example, only two of the five monocyclic cytosine analogues, analogues 4 and 6 (Figure 2), demonstrated immunostimulatory activity. Thus, the result yielded by the analogue 7 P-base species does not clearly and absolutely teach away from all other species within the genus of P-base cytosine analogues (Applicant's argument) because Applicant clearly teaches that other species of similar structure should be tested as there are other isostructural cytosine analogue species from which the ordinary artisan may reasonably expect (at least 40% probability of success, as per 2/5 of the monocyclic cytosine analogues) to detect immunostimulatory activity when assayed under the appropriate conditions. Krieg disclosed immunostimulatory oligonucleotides in which the cytosine of a CpG motif is substituted for a P-base and the guanosine may be substituted for a purine base analog of guanine, e.g. 7-deazaguanine. The pyrimidine base analog of cytosine can replace cytosine without impairing the immunostimulatory activity of the oligonucleotide. Similarly, the modified guanine can replace guanine without impairing immunostimulatory activity [0094]. Wise et al disclosed that the pyrrolocytosine can substitute for cytosine without substantially altering the properties of nucleosides in which cytosine would normally be present. That is, replacement of cytosine with pyrrolopyrimidine-C does not substantially affect the functioning of the nucleoside in any substantial manner. Thus, replacement of cytosine with pyrrolopyrimidine-C is not believed to substantially alter the structure, e.g., secondary, tertiary or other structure, of any nucleic acid strand which substitutes one or more cytosines with one or more pyrrolopyrimidine-C molecules. Such properties provide for the ability to use pyrrolopyrimidine-C in place of cytosine in many applications, such as…investigation of nucleic acid-protein interactions, investigation of nucleoside-protein interactions, for therapeutic uses, and the like [0007]. Liu et al teach the artisan a means of assaying physical/structural properties

[nucleic acid-protein interactions] which complements the functional assays taught by Yu et al and Kandimalla et al. Thus, the use of pyrrolocytosine (Liu, Wise) would have logically commended itself to an inventor's attention (Yu, Kandimalla, Krieg) because it advantageously provides a means of detecting nucleic acid-protein interactions when measuring an immune stimulatory response, regardless of the magnitude of the immunostimulatory response. The claims require no minimum immunostimulatory response, and thus any response, however small, will meet the limitations of the claim. Based on the preponderance of evidence in the record, the Examiner maintains the position that, at the time of the invention, those of ordinary skill in the art had both taught, suggested and possessed a reasonable expectation of success that an immunostimulatory oligonucleotide comprising a C*pG motif in which the cytosine (C*) is substituted for the cytosine analogue, P-base pyrrolocytosine (a.k.a. 2-oxo-7-deaza-8-methyl-purine) would retain immunostimulatory activity, per the intended use.

Applicant continues to argue that Liu is non-analogous art because the teachings of Liu are directed to the intended use of the instantly claimed oligonucleotide. The field of the present invention is oligonucleotide-based compounds that are immunostimulatory in mammalian systems. The intended use and/or purpose of Liu is to gain "an understanding of the nature of the melted bubble which moves with the RNA polymerase active site" during transcription elongation.

Applicant's argument(s) has been fully considered, but is not persuasive. "Under the correct analysis, any need or problem known in the field of endeavor at the time of the invention and addressed by the patent [or application at issue] can provide a reason for combining the elements in the manner claimed. " *KSR International Co. v. Teleflex Inc.*, 550 U.S. ___, ___, 82 USPQ2d 1385, 1397 (2007). Thus a reference in a field different from that of applicant's endeavor may be reasonably pertinent if it is one which, because of the matter with which it deals, logically would have commended itself to an inventor's attention in considering his or her invention as a whole. See MPEP §2141.01(a).

It is proper to "take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741,82 USPQ2d

1385, 1396 (2007). See also Id. At 1742, 82 USPQ2d 1397 ("A person of ordinary skill is also a person of ordinary creativity, not an automaton.").

Liu et al is considered analogous art for teaching that pyrrolocytosine is advantageous and ideal for probing protein-nucleic acid interactions.

Yu et al teach that their laboratory has been studying the impact of chemical modifications on the immunostimulatory activity of CpG oligos. Similarly, Kandimalla et al teach that the mechanism of immunostimulation by CpG-oligonucleotides and the precise structural requirements and specific functional groups of cytosine and guanine necessary for recognition of and interaction with protein/receptor factors [protein-nucleic acid interaction] that are responsible for immune stimulation have not been elucidated.

With regard to substituting equivalents known in the prior art for the same purpose: Kandimalla et al taught the substitution of a cytosine in a CpG motif for a P-base for the same purpose: the intention to elicit an immune stimulatory response. Krieg disclosed immunostimulatory oligonucleotides in which the cytosine of a CpG motif is substituted for a P-base. The pyrimidine base analog of cytosine can replace cytosine without impairing the immunostimulatory activity of the oligonucleotide [0094]. Wise et al disclosed that the pyrrolocytosine can substitute for cytosine without substantially altering the properties of nucleosides in which cytosine would normally be present. That is, replacement of cytosine with pyrrolopyrimidine-C does not substantially affect the functioning of the nucleoside in any substantial manner. Thus, replacement of cytosine with pyrrolopyrimidine-C is not believed to substantially alter the structure, e.g., secondary, tertiary or other structure, of any nucleic acid strand which substitutes one or more cytosines with one or more pyrrolopyrimidine-C molecules. Such properties provide for the ability to use pyrrolopyrimidine-C in place of cytosine in many applications, such as…investigation of nucleic acid-protein interactions, investigation of nucleoside-protein interactions, for therapeutic uses, and the like [0007]. Liu et al teach the artisan a means of assaying physical/structural properties [nucleic acid-protein interactions] which complements the functional assays taught by Yu et al and Kandimalla et al. Thus, the use of pyrrolocytosine (Liu, Wise) would have logically commended itself to an inventor's attention because it advantageously provides a means of detecting nucleic acid-protein interactions when measuring an immune stimulatory response (Yu, Kandimalla, Krieg), regardless of the

magnitude of the immunostimulatory response. The claims require no minimum immunostimulatory response, and thus any response, however small, will meet the limitations of the claim. Based on the preponderance of evidence in the record, the Examiner maintains the position that, at the time of the invention, those of ordinary skill in the art had both taught, suggested and possessed a reasonable expectation of success that an immunostimulatory oligonucleotide comprising a C*pG motif in which the cytosine (C*) is substituted for the cytosine analogue, P-base pyrrolocytosine (a.k.a. 2-oxo-7-deaza-8-methyl-purine) would retain immunostimulatory activity, per the intended use.

Applicant argues that the intended use of the instantly claimed invention is to generate an immune response; specifically, the instantly claimed immunomers are used to modify and/or enhance the immune response as compared to oligonucleotides having a wild-type CpG dinucleotide. The intended use of Liu is to use the intrinsically high fluorescence of pyrrolo-dC to gain "an understanding of the nature of the melted bubble which moves with the RNA polymerase active site" during transcription elongation. Liu teaches the incorporation of pyrrolo-dC into duplex DNA and the formation of the elongation bubble which moves with the RNA polymerase active site. it is this melting of the duplex DNA into single-stranded DNA that increases the fluorescence of pyrrolo-dC and not any DNA-protein interaction. As such, the fluorescent properties of pyrrolo-dC would be completely useless in the instant technological field as the instantly claimed compounds are single-stranded. There would be no change in the fluorescence levels of pyrrolo-dC regardless of whether the instantly claimed compound was interacting with the target receptor or not. Therefore, the use of pyrrolo-dC as taught by Liu would provide absolutely no useful information to one skilled in the art regarding the interaction between a CpG-containing oligonucleotide and its target protein receptor.

Applicant's argument(s) has been fully considered, but is not persuasive. Arguments of counsel cannot take the place of **factually supported objective evidence** in the record. See *In re Schulze*, 346 F.2d 500, 602, 145 USPQ 716, 718 (CCPA 1965), *In re Huang*, 100 F.3d 135, 139-40, 40 USPQ2d 1685, 1689 (Fed. Cir. 1996); *In re De Blauwe*, 736 F.2d 699, 705, 222 USPQ 191, 196 (Fed. Cir. 1984). Attorney statements regarding, e.g. the fluorescent properties of pyrrolo-dC would be **completely useless** [emphasis added] in the instant technological field as

the instantly claimed compounds, that **there would be no change in the fluorescence levels** [emphasis added] of pyrrolo-dC regardless of whether the instantly claimed compound was interacting with the target receptor or not, and that the use of pyrrolo-dC as taught by Liu would provide **absolutely no useful information** [emphasis added] to one skilled in the art regarding the interaction between a CpG-containing oligonucleotide and its target protein receptor, are not evidence without a supporting declaration.

Applicant argues that Krieg (U.S. Patent 6,207,646) taught that mitogenic ODN sequences uniformly became nonstimulatorv if the CpG dinuclcotide was mutated.

Applicant's argument(s) has been fully considered, but is not persuasive.

As a first matter, Krieg (U.S. Patent 6,207,646) is not one of the references cited in the rejection. Furthermore, Krieg is silent regarding the use of P-base cytosine analogs in the context of immunostimulatory oligonucleotides.

As a second matter, Krieg's later work (U.S. 2004/0053880) disclosed immunostimulatory oligonucleotides in which the cytosine of a CpG motif is substituted for a P-base and the guanosine may be substituted for a purine base analog of guanine, e.g. 7-deazaguanine. The pyrimidine base analog of cytosine can replace cytosine without impairing the immunostimulatory activity of the oligonucleotide. Similarly, the modified guanine can replace guanine without impairing immunostimulatory activity [0094]. Thus, at the time of the invention, those of ordinary skill in the art possessed a reasonable [emphasis added] expectation of success for an immunostimulatory oligonucleotide comprising 2-oxo-7-deaza-8-methyl-purine to retain immune stimulatory activity.

Double Patenting

4. **Claim 1 stands rejected** on the ground of nonstatutory obviousness-type double patenting over Claim 1 of copending Application No. 10/361,111 (U.S. 2004/0156825), now U.S. Patent 7,354,907.

Although the conflicting claims are not identical, they are not patentably distinct from each other because they both claim immunomers having at least two oligonucleotides linked together by a non-nucleotidic linker, wherein the internucleoside linkage is modified, wherein at least one of the oligonucleotides is an oligonucleotide having an accessible 5' end and comprising an immunostimulatory dinucleotide having the structure of a non-natural pyrimidine nucleoside and a non-natural purine nucleoside. Thus, although the subject matter is recited

using different terms, the composition(s) of the instant claim(s) is reasonably embraced and anticipated by the composition(s) recited in the patent.

5. **Claims 1 and 31 stand provisionally rejected** on the ground of nonstatutory obviousness-type double patenting over Claim 18 of copending Application No. 10/865,245.

Although the conflicting claims are not identical, they are not patentably distinct from each other because they both claim immunostimulatory oligonucleotide compositions comprising an immunostimulatory dinucleotide having the structure of a non-natural pyrimidine nucleoside and a non-natural purine nucleoside.

The claims are drawn to an immunostimulatory oligonucleotide compound comprising a "CpG" motif, wherein the "C" moiety is a non-natural pyrimidine and the "G" moiety is a natural or non-natural pyrimidine nucleoside, wherein the immunostimulatory oligonucleotides may be joined by 3' to 3' linkages. Thus, instantly claimed immunomer composition(s) are reasonably embraced by immunostimulatory oligonucleotide(s) of the copending application. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

6. **Claims 1 and 31 stand provisionally rejected** on the ground of nonstatutory obviousness-type double patenting over Claims 11-13 and 16 of copending Application No. 11/153,054.

Although the conflicting claims are not identical, they are not patentably distinct from each other because they both claim immunostimulatory oligonucleotide compositions comprising an immunostimulatory dinucleotide having the structure of a non-natural pyrimidine nucleoside and a non-natural purine nucleoside.

Because the claims of copending Application No. 11/153,054 recite generically "CpG, C*pG, C*pG* and CpG*", the Examiner has looked to the specification for definitions of the "C" and "G" moieties so as to better understand the invention. The specification discloses that C* is… 1-(2'-deoxy-β-D-ribofuranosyl)-2-oxo-7-deaza-8-methyl-purine, and that G* is… 2'-deoxy-7-deazaguanosine (pg 1, [0010]), wherein the non-nucleotidic linker may be a 3'-3' linkage (pg 3, [0032]). Thus, instantly claimed immunomer composition(s) anticipate immunostimulatory oligonucleotide(s) of the copending application.

This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

7. **Claims 1 and 31 stand provisionally rejected** on the ground of nonstatutory obviousness-type double patenting over Claims 1 and 4 of copending Application No. 11/174,002 (U.S. 2006/0211641).

Although the conflicting claims are not identical, they are not patentably distinct from each other because they both claim immunostimulatory oligonucleotide compositions comprising an immunostimulatory dinucleotide having the structure of a non-natural pyrimidine nucleoside and a natural or non-natural purine nucleoside.

Thus, instantly claimed immunomer composition(s) anticipate immunostimulatory oligonucleotide(s) of the copending application.

This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

Response to Arguments

Applicant argues that Applicants will consider filing a Terminal Disclaimer or take any other action deemed necessary in the later filed, copending applications 10/361,111, 10/865,245, 11/153,054 and 11/174,002.

Applicant's argument(s) has been fully considered, but is not persuasive. Applicant has not filed a Terminal Disclaimer or taken any other action deemed necessary in the later filed, copending applications as it pertains to the instant application. The provisional nonstatutory obviousness-type double patenting rejections will be maintained until all claims have been deemed otherwise in condition for allowance or allowable.

Conclusion

8. No claims are allowed.

The prior art made of record and not relied upon is considered pertinent to Applicant's disclosure:

Fearon et al (U.S. Patent 7,255,868) disclosed immunostimulatory nucleic acids comprising CpG motifs, wherein the cytosine may be substituted with an isostructural bicyclic analog (col. 30, line 45-col. 31, line 40).

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Kevin K. Hill whose telephone number is 571-272-8036. The Examiner can normally be reached on Monday through Friday, between 9:00am-6:00pm EST.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Joseph T. Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Kevin K. Hill/
Examiner, Art Unit 1633